ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

FEATURED CLINICAL TRIAL

*PREVEN*tion of HeartMate II Pump *T*hrombosis Through Clinical Management: The PREVENT multi-center study

Simon Maltais, MD, PhD,[a] Ahmet Kilic, MD,[b] Sriram Nathan, MD,[c] Mary Keebler, MD,[d] Sitaramesh Emani, MD,[e] John Ransom, MD,[f] Jason N. Katz, MD,[g] Brett Sheridan, MD,[h] Andreas Brieke, MD,[i] Gregory Egnaczyk, MD,[j] John W. Entwistle III, MD, PhD,[k] Robert Adamson, MD,[l] John Stulak, MD,[a] Nir Uriel, MD,[m] John B. O'Connell, MD,[n] David J. Farrar, PhD,[n] Kartik S. Sundareswaran, PhD,[n] Igor Gregoric, MD[c] and on behalf of the PREVENT Study Investigators

From the [a]Division of Cardiovascular Surgery, Mayo Clinic, Rochester, Minnesota; [b]Division of Cardiac Surgery, Ohio State University Medical Center, Columbus, Ohio; [c]Memorial Hermann–Texas Medical Center, Houston, Texas; [d]Vanderbilt Heart and Vascular Institute, Vanderbilt University, Nashville, Tennessee; [e]Division of Cardiovascular Medicine, Ohio State University Medical Center, Columbus, Ohio; [f]Baptist Health Heart and Transplant Institute, Little Rock, Arkansas; [g]Division of Cardiology and [h]Division of Cardiothoracic Surgery, University of North Carolina, Chapel Hill, North Carolina; [i]University of Colorado School of Medicine, Denver, Colorado; [j]Christ Hospital, Cincinnati, Ohio; [k]Thomas Jefferson University, Philadelphia, Pennsylvania; [l]Sharp Memorial Hospital, San Diego, California; [m]University of Chicago Medical Center, Chicago, Illinois; and the [n]St. Jude Medical, Inc., Pleasanton, California.

KEYWORDS:
HeartMate II;
pump thrombosis;
prevention;
best practices;
continuous-flow left ventricular assist device (CF-LVAD)

BACKGROUND: Recommended structured clinical practices including implant technique, anti-coagulation strategy, and pump speed management (PREVENT [*PREVEN*tion of HeartMate II Pump *T*hrombosis Through Clinical Management] recommendations) were developed to address risk of early (<3 months) pump thrombosis (PT) risk with HeartMate II (HMII; St. Jude Medical, Inc. [Thoratec Corporation], Pleasanton, CA). We prospectively assessed the HMII PT rate in the current era when participating centers adhered to the PREVENT recommendations.

METHODS: PREVENT was a prospective, multi-center, single-arm, non-randomized study of 300 patients implanted with HMII at 24 participating sites. Confirmed PT (any suspected PT confirmed visually and/or adjudicated by an independent assessor) was evaluated at 3 months (primary end-point) and at 6 months after implantation.

RESULTS: The population included 83% men (age 57 years ± 13), 78% destination therapy, and 83% Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Profile 1–3. Primary end-point analysis showed a confirmed PT of 2.9% at 3 months and 4.8% at 6 months. Adherence to key recommendations included 78% to surgical recommendations, 95% to heparin bridging, and 79% to pump speeds ≥9,000 RPMs (92% >8,600 RPMs). Full adherence to implant techniques, heparin bridging, and pump speeds ≥9,000 RPMs resulted in a significantly lower risk of PT (1.9% vs 8.9%; $p < 0.01$) and lower

Reprint requests: Simon Maltais, MD, PhD, Department of Cardiovascular Surgery, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905. Telephone: 507-255-7064. Fax: 507-255-8674.

E-mail address: Maltais.Simon@mayo.edu

http://dx.doi.org/10.1016/j.healun.2016.10.001

composite risk of suspected thrombosis, hemolysis, and ischemic stroke (5.7% vs 17.7%; $p < 0.01$) at 6 months.

CONCLUSIONS: Adoption of all components of a structured surgical implant technique and clinical management strategy (PREVENT recommendations) is associated with low rates of confirmed PT.

J Heart Lung Transplant 2017;36:1–12

The evolution of left ventricular assist device (LVAD) therapy has resulted in a durable option for patients with advanced heart failure refractory to optimal medical management as either a bridge to transplantation (BTT) or destination therapy (DT). Outcomes with current continuous-flow devices continue to demonstrate significant patient benefit not only in enhanced survival but also improved functional capacity and quality of life.[1] Although the improvement of survival over time has resulted in a more widespread adoption of this therapy, adverse events persist, including, most notably, infection, bleeding, and pump thrombosis (PT).[2] Beginning in 2011, some centers and collaborative groups began to observe a significant increase in the incidence of PT with the HeartMate II (HMII; St. Jude Medical, Inc. [Thoratec Corporation], Pleasanton, CA) LVAD.[3,4] The observed increase in PT raised concerns within the scientific community and prompted further evaluation among implanting centers, the results of which revealed variability in thrombosis rates during the same period.[5,6] Not limited to the HMII device, other commercially approved continuous-flow LVADs have also experienced PT events, where blood pressure control and anti-coagulation have been identified as risk factors for PT.[7]

Reasons for the observed increase in PT rates were unclear but were thought to be multi-factorial. Initial clinical experience with HMII highlighted a high incidence of gastrointestinal bleeding, which was partially attributed to the presence of acquired von Willebrand factor deficiency in continuous-flow LVAD recipients.[8,9] This may have led to the adoption of lower anti-coagulation to prevent gastrointestinal bleeding at some institutions. Concomitantly, associations between aortic valve opening and aortic regurgitation were observed, which may have prompted lowering of pump speeds to facilitate greater flow through the aortic valve.[10] Furthermore, mechanical issues related to the pump position (inflow cannula obstruction and/or outflow graft kinking) and their potential association with PT identified variability in HMII implantation.[11,12] This variability in pump implantation led to the development of surgical principles aimed at reducing the risk of inflow cannula malposition and subsequent pump migration.[13–15]

Changes in patient management, including strict adherence to an international normalized ratio (INR) of 2–3, early initiation of aspirin therapy (81–325 mg), and use of perioperative heparin, have been reported to decrease the rate of device exchange secondary to PT by >50%.[6] Shared experiences among centers with favorable outcomes led to the development of practices to reduce the risk of PT. These practices were similar to the recommendations in the HMII instructions for use, with modifications derived from clinical practice.[15] The PREVENT (*PREVEN*tion of HeartMate II Pump *T*hrombosis Through Clinical Management) study was designed to evaluate the rates of PT when these management practices were adopted.

Methods

Study design

The PREVENT study was a prospective, multi-center, non-randomized study that sought to evaluate outcomes in patients with the adoption of recommended practices aimed at reducing the risk of PT (PREVENT recommendations). These practices specifically focused on implantation technique, anti-coagulation regimen, pump speed, and blood pressure management (Table 1). The primary end-point of the study was confirmed PT (as defined in Table 2) at 3 months after implantation. Secondary end-points included the incidence of pre-defined adverse events, survival, and the level of adherence to recommended practices evaluated through 6 months of support. The study hypothesis was a confirmed rate of early PT $\leq$4% at 3 months with the implementation of recommended practices. This rate was based on the 7-center reported rate of 3.9%,[15] from which portions of the PREVENT recommendations were derived. A sample size of 300 patients provided 94% power to detect a statistically significant difference between a 3-month PT rate of 8.4% (reported by Starling et al[3]) and the 4% rate expected from this study. The study was conducted at 24 centers across the United States, with 23 centers contributing at least 1 patient to the study.

Center selection

Centers were selected based on the following criteria: (1) willingness to adopt the study management practice recommendations; (2) ability to enroll at least 15 patients into the study over a 9-month time frame; (3) expectation that the center would not start enrolling into the HeartMate 3 (HM3)/MOMENTUM 3 clinical trial[16] within 9 months of PREVENT study initiation or was not 1 of the original 60 HM3 sites (to avoid preferential enrollment bias of sicker patients into PREVENT when the HM3 clinical trial was ongoing); and (4) geographically represented around the United States. Thrombus rates did not factor into the site selection. At the time of PREVENT study initiation, the suspected thrombosis rate at 3 and 6 months at PREVENT sites was 6.1% and 9.8%, respectively, which was not different from the suspected thrombosis rate at non-PREVENT sites (6.9% and 9.9%, respectively). Non-PREVENT sites included all centers implanting

Table 1 Overview of PREVENT Surgical Recommendations

Surgical recommendations

1. Create an adequately sized pump pocket, located inferiorly deep and lateral.
2. Position the inflow cannula parallel to the septum, oriented to the central left ventricle.
3. Position the outflow graft right of the sternal midline to avoid compression of the right ventricle.
4. Position the pump below the diaphragm.
5. Fixate the pump (e.g., to the diaphragm or the chest wall) to prevent migration.

Anti-coagulation and anti-platelet management

1. In patients without persistent bleeding, begin bridging with unfractionated heparin or LMWH within 48 hours of device implantation with a goal PTT of 40–45 seconds in the first 48 hours, followed by titration up to PTT of 50–60 seconds by 96 hours. If heparin is contraindicated, consider other alternatives, including argatroban, intravenous warfarin, and bivalirudin.
2. Initiate warfarin within 48 hours to obtain goal INR of 2.0–2.5 by post-operative days 5–7, at which time heparin therapy may be discontinued.
3. When there is no evidence of bleeding, initiate aspirin therapy (81–325 mg daily) 2–5 days after HMII implantation.
4. Maintain the patient throughout LVAD support on aspirin and warfarin with goal INR of 2.0–2.5.

Pump speed management

1. Run pump speeds $>$9,000 RPM, and avoid speeds $<$8,600 RPM.
2. Adjust pump speed to permit intermittent aortic valve opening only after above goals are achieved.

Blood pressure management

1. Maintain a MAP $<$90 mm Hg.

HMII, HeartMate II; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LVAD, left ventricular assist device; MAP, mean arterial pressure; PTT, partial thromboplastin time.

the HMII not participating the PREVENT study. The thrombus rate was evaluated over a 2-year implanting period from October 1, 2012, through September 19, 2014, based on events reported to Thoratec Corporation and the US Food and Drug Administration within the first 6 months of implantation. During that period, 1,149 HMIIs were implanted at PREVENT sites, and 5,921 HMIIs were implanted at non-PREVENT sites.

Enrollment into the PREVENT study was between September 24, 2014, and November 5, 2015. Follow-up of subjects was through 6 months post-implant. Five centers enrolled 20–34 subjects, 10 centers enrolled 10–19 subjects , and 8 centers enrolled 2–9 subjects. The trial was designed by the sponsor (St. Jude Medical, Inc [Thoratec Corporation]) and reviewed by an independent protocol review committee, whose inputs were

Table 2 Definition of Pump Thrombosis

Pump thrombosis is an event in which the pump or its conduits contain a thrombus that results in or could potentially induce circulatory failure.

Suspected pump thrombus is an event in which clinical or mechanical circulatory support device parameters suggest thrombus in the blood contacting components of the pump, cannulae, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:

1. Presence of hemolysis (clinical hemolysis and/or sustained LDH $>$3.0 upper laboratory normal limit)
2. Worsening heart failure (or lack of left ventricular unloading when a ramp test is performed)
3. Abnormal pump parameters (elevated pump powers $>$10 W or 2 W higher than baseline)

Suspected pump thrombus should be accompanied by $\geq$1 of the following events or interventions:

1. Treatment with intravenous anti-coagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous anti-platelet therapy (e.g., eptifibatide, tirofiban)
2. Pump replacement
3. Pump explantation
4. Urgent transplantation (UNOS status 1A)
5. Stroke
6. Death

Confirmed pump thrombus: A suspected pump thrombosis event in which a thrombus is confirmed in the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported via direct visual inspection (documented by a photograph if available) on pump explantation or by sending the pump back to Thoratec/St. Jude Medical for evaluation. Any pump explanted for suspected device thrombosis should be sent back to Thoratec/St. Jude Medical for analysis. All pump thrombosis events will be adjudicated by an independent committee.

LDH, lactate dehydrogenase; tPA, tissue plasminogen activator; UNOS, United Network for Organ Sharing.

captured into the protocol. Coordinators at each site collected all data, which were entered into an electronic data capture system for analysis by the sponsor. Participating sites were monitored to ensure that all data were entered into the electronic data capture system. The academic authors had independent access to the data and vouch for the completeness and accuracy of the data and the analyses. The institutional review board at each participating center approved the protocol.

PREVENT recommendations and adherence tracking

The practices recommended as part of the PREVENT study were aimed at maximizing flow through the LVAD, reducing risk of cannula malposition, and ensuring that the patient was adequately anti-coagulated while on LVAD support.[11] The recommendations are summarized in Table 1. The study expected all centers to adopt and adhere to the recommendations in principle; however, the protocol allowed for deviations as deemed necessary by clinical judgment for specific scenarios. For example, patients with a previous thromboembolic event or at risk of a thromboembolic event (e.g., presence of a mechanical heart valve) could be managed with a higher INR target and/or with additional anti-platelet therapy. Similarly, patients with bleeding events or at a higher risk of bleeding could use a lower target anti-coagulation and/or reduced anti-platelet therapies. Patients who had small ventricles or right heart failure were permitted to have pump speeds $<$9,000 RPMs. Adherence to the recommended practices were tracked over the course of the clinical study, and reasons for deviation were documented.

Study subjects

All consecutive subjects receiving HMII in accordance with the Food and Drug Administration–approved indications regardless of indication (BTT or DT), sex, race, or ethnicity who gave consent were considered for the study. Additional inclusion criteria were (1) subject was receiving HMII as his or her first LVAD and (2) age $\geq$18 years. The exclusion criteria were (1) existence of ongoing mechanical circulatory support (other than intraaortic blood pump), (2) pregnancy, or (3) participation in any other clinical trial investigations that would have confounded results of the study. The study sought to enroll a real-world ventricular assist device patient population.

Time points for data collection were pre-implant (baseline), at implantation, at 1 week post-implant, and at months 1, 3, and 6 post-implant. Follow-up data included adherence to the recommendations, subject outcome, laboratory assessments, hemodynamics, and echocardiogram results. INR values, lactate dehydrogenase (LDH) levels, and changes to anti-coagulation/anti-platelet medications were collected and logged continuously throughout the trial. Chest x-rays were collected immediately after implantation as well as at 6 months after implantation. Data pertaining to adverse events, rehospitalizations, and operative procedures were collected as they occurred.

Adverse event definitions

Standard Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions (version 3.0) of adverse events were used in this study.[17] All PT events (suspected or confirmed) were adjudicated by an independent committee as per the definition outlined in Table 2. In situations in which pumps were not explanted for suspected thrombosis or if patient support was still ongoing, the adjudication committee made the determination if the event should be counted as confirmed or unconfirmed PT based on available LDH and outcome data.

Statistical analysis

The primary end-point was analyzed as a calculated percentage of total implants with confirmed PT at 3 months after implantation. All secondary end-points including survival and adverse events were evaluated through 6 months post-implantation. Categorical data are presented as a proportion, and continuous variables are presented as mean $\pm$ SD or median (range, interquartile range [IQR]) as appropriate. Comparisons of categorical variables between 2 groups were performed using Fisher's exact test, whereas comparisons of continuous variables were performed using either Student's *t*-test (if normally distributed) or Wilcoxon's rank-sum test (if non-normally distributed). Time to event analysis was performed using the Kaplan-Meier method, and comparisons between the 2 groups were made using the log-rank method. All statistical comparisons were 2-sided (unless otherwise stated), and a p-value of < 0.05 was considered to be statistically significant. The statistical analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

Results

Patient characteristics

The study enrolled 300 patients at 23 centers (Table 3). Most of the patients were male (83%) with an average age of 57 years $\pm$ 13. Patient characteristics were typical of patients with advanced heart failure receiving an LVAD. A higher proportion of patients received HMII as DT (78%) than BTT. The 300 patients received 307 devices within the first 3 months of initial implantation and 314 devices within the first 6 months. The left atrial appendage was closed in 21 patients (7%).

PT and overall outcomes

The primary end-point rate of confirmed PT at 3 months was 2.9% (9/307), with 12 suspected or confirmed events in 11 patients (3.6%). Figure 1A shows a summary of early PT events associated with the primary end-point of the study. There were 12 suspected thrombosis events, of which 9 were confirmed, in 11 patients (3.6%). Figure 2 shows an example of a suspected thrombosis event that was confirmed (Figure 2A) and an example of suspected PT that was not confirmed (Figure 2B). Major hemolysis was absent in all 3 cases of suspected, but not confirmed, PT (2 were suspected because of power elevations and heart failure and 1 because of LDH elevation and a failed ramp test).

Figure 1B shows a summary of all suspected PT events within 6 months (including events in the first 3 months) of implantation (total follow-up duration). There were 20 suspected PT events, of which 15 were confirmed (5.0% of patients, 4.8% of pumps), in 18 patients (6.0%). No thrombus was found on explant analysis in 3 cases. In 2 cases, the patient was still ongoing on LVAD support, and the event resolved with medical intervention. In 1 case, the

Table 3 Key Baseline Characteristics of Subjects Enrolled in PREVENT Study

Clinical Variables	Value ($N = 300$)
Age, years	57 ± 13
Female	52 (17%)
BTT/DT	66 (22%)/234 (78%)
NYHA class IV	258 (86%)
INTERMACS profiles	
Profile 1	38 (13%)
Profile 2	90 (30%)
Profile 3	121 (40%)
Profile 4–7	51 (17%)
Left ventricular ejection fraction, %	18 ± 6
Ischemic cardiomyopathy	139 (46%)
Atrial fibrillation	94 (31%)
Presence of left atrial thrombus	4 (1.3%)
Presence of left ventricular thrombus	14 (5%)
BSA, m^2	2.11 ± 0.29
BMI, kg/m^2	29.4 ± 6.3
BMI ≥35	47 (16%)
Presence of hypercoagulable disorder	46 (15%)
History of valve procedures	20 (7%)
ACE inhibitor use	76 (25%)
Beta-blocker use	166 (55%)
Inotropes	231 (77%)
IABP	87 (29%)
Laboratory values	
BUN, mg/dl	29.6 ± 15.4
Creatinine, mg/dl	1.46 ± 0.78
Albumin, g/dl	3.47 ± 0.67
AST, U/liter	40 ± 59
ALT, U/liter	58 ± 106
Total bilirubin, mg/dl	1.26 ± 1.04
Pre-implant hemodynamics	
BP systolic, mm Hg	105 ± 15
BP diastolic, mm Hg	65 ± 11
CVP, mm Hg	12.1 ± 7.0
Systolic PAP, mm Hg	51.6 ± 14.9
Diastolic PAP, mm Hg	26.1 ± 8.7
Mean PAP, mm Hg	35.6 ± 10.7
PCWP, mm Hg	24.0 ± 8.9
Cardiac index, $liter/min/m^2$	1.96 ± 0.56
CVP/PCWP, mm Hg	0.50 ± 0.27

ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BMI, body mass index; BSA, body surface area; BTT, bridge to transplantation; BUN, blood urea nitrogen; CVP, central venous pressure; DT, destination therapy; IABP, intraaortic blood pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.
Values are presented as mean ± SD or number (%).

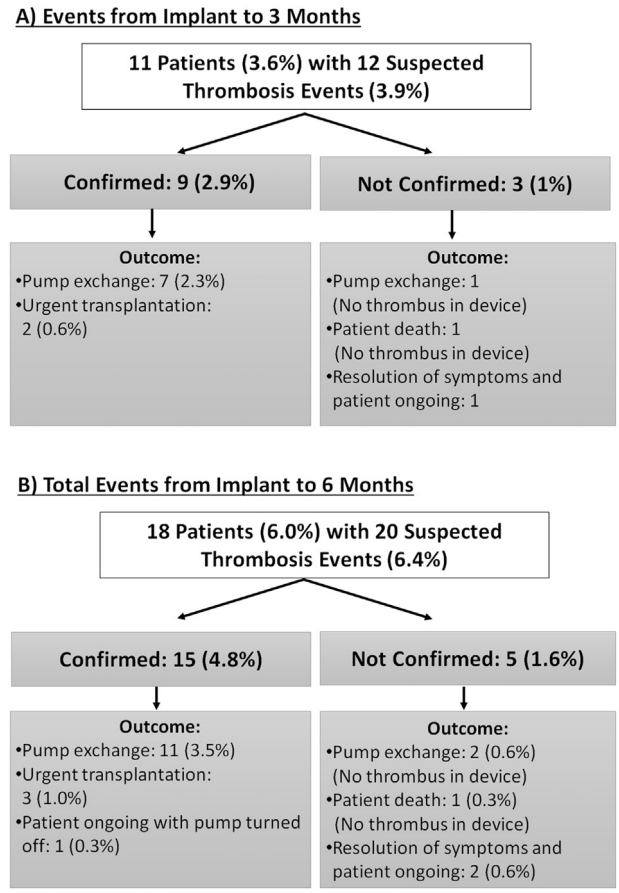

Figure 1 (A) Overview of early (<3 months) PT events (primary end-point); 300 subjects received 307 devices within first 3 months of implantation. Adjudication of confirmed thrombosis was performed by 2 independent physicians based on detailed evaluation of all available clinical evidence including (but not limited to) LDH, echocardiography reports, symptoms of PT, and pump explant analyses (if available). (B) Overview of all PT events within the first 6 months after implantation; 300 subjects received 314 devices over 6 months.

patient had the pump turned off and was ongoing with the original pump still implanted, but turned off. The patient was managed with heart failure medications. Explant analysis was conducted in 16 of the 20 suspected PT cases. In the 4 cases in which no explant analysis was performed (3 cases with the pump still implanted with the patient alive and 1 case of pump exchange in which the pump was not returned), 2 were identified to be cases of confirmed pump thrombus based on other available evidence (significant hemolysis, log-file assessment). In the remaining 2 cases, thrombus could not be confirmed, as the patient was still ongoing and all available evidence could not point to thrombus present in the device. In 13 patients, a pump exchange for suspected thrombosis was performed (12 were HMII to HMII, 1 was HMII to HVAD [HeartWare, Framingham, MA), of which 11 had confirmed thrombus; thrombus was not confirmed in the other 2 patients. Two patients with confirmed PT died. One patient died 11 days after exchange as a result of a complication associated with an aortic dissection that worsened at the time of pump exchange. The second patient died 88 days after PT exchange, and the cause of death was right hydropneumothorax.

Overall survival at 6 months was 89% ± 2 (Figure 3A), and survival free of PT was 84% ± 2 (Figure 3B). By 6 months, 14 patients (5%) had received heart transplants,

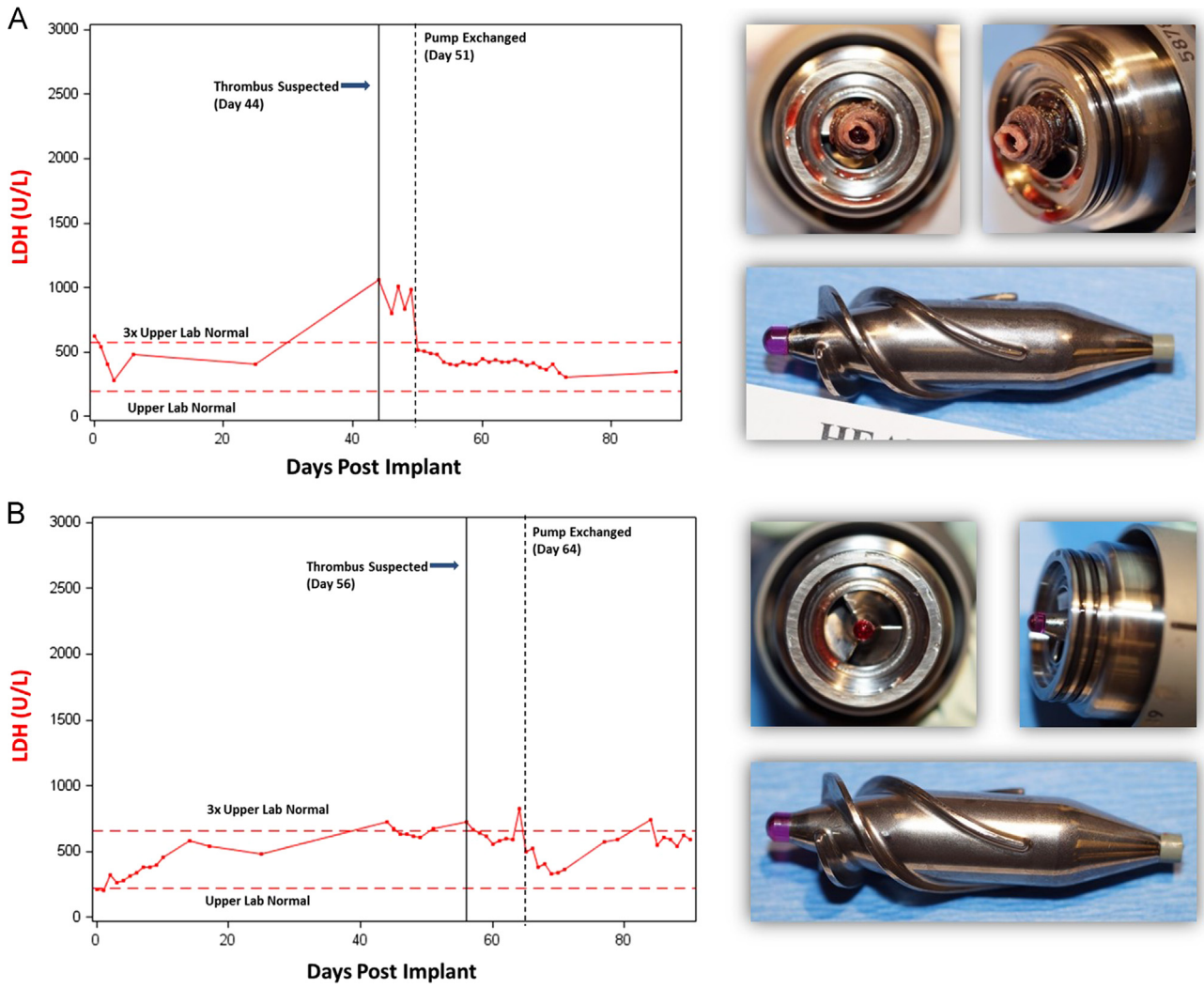

Figure 2 (A) Example of a confirmed PT event. (B) Example of a suspected but not confirmed PT event.

3 related to PT and 11 independent of PT. Survival of BTT patients was 92.4% ± 3.3 and of DT patients was 87.8% ± 2.2, with no difference between the groups. There was no statistically significant difference in survival between patients with and without PT (80.8% ± 12.2 vs 89.0% ± 1.9; $p = 0.70$).

Adverse events

Table 4 shows the adverse events experienced by patients over the duration of the study. The overall incidence of all forms of bleeding was 45% at 6 months, with 21% of the patients experiencing a gastrointestinal bleeding event.

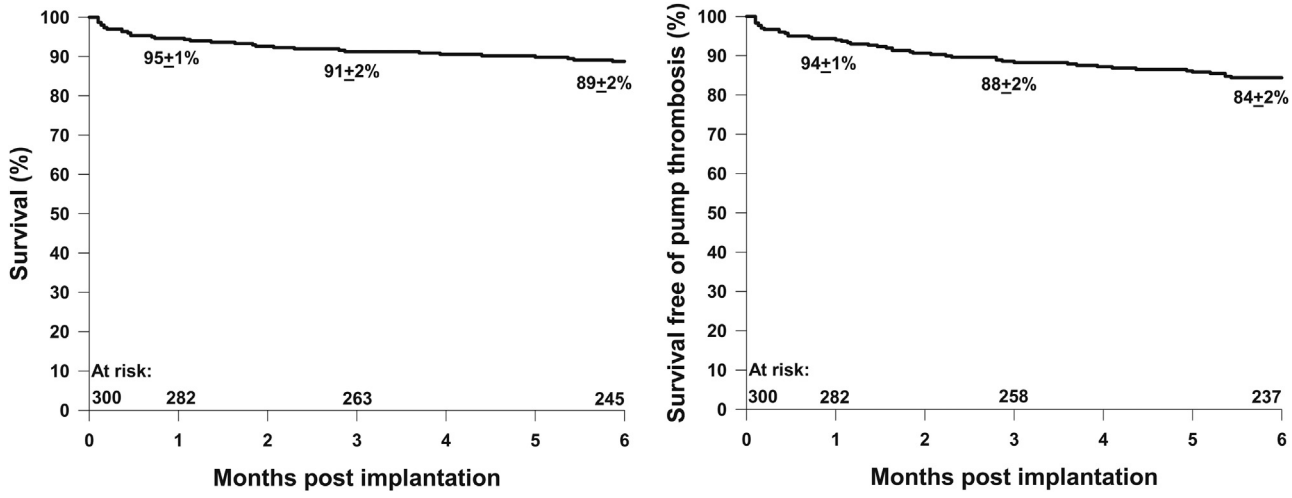

Figure 3 Overall survival and survival free of confirmed PT.

Table 4 Adverse Events (Besides Pump Thrombosis) at 6 Months After Implantation

Adverse event	Incidence at 6 months ($N = 300$)
Overall bleeding	134 (45%)
Bleeding requiring surgery	49 (16%)
Early bleeding ($\leq$30 days)	101 (34%)
GI bleeding	64 (21%)
Right heart failure	49 (16%)
RVAD use	14 (5%)
Any infection	83 (28%)
Driveline infection	14 (5%)
Ischemic stroke	12 (4%)
Hemorrhagic stroke	8 (2.7%)
Hemolysis	20 (6.7%)
Concurrent with PT	13 (4.3%)
Isolated hemolysis that resolved with treatment and no suspected PT	7 (2.3%)

GI, gastrointestinal; PT, pump thrombosis; RVAD, right ventricular assist device.

Bleeding requiring surgery occurred in 16% of the patients, and early post-operative bleeding (<30 days) occurred in 34% of all patients. There was no significant difference in suspected PT at 6 months between patients who had an early bleeding event (4.9%) and patients who did not (6.5%; $p = 0.80$). None of the patients who had aspirin therapy stopped or warfarin temporarily stopped for early bleeding had a subsequent PT event. Ischemic stroke occurred in 4% of patients, and hemorrhagic stroke occurred in 2.7%. The incidence of right heart failure was 16% with 5% requiring a right ventricular assist device (all early except for 1 case in which a right ventricular assist device was required late after 5.5 months). The overall incidence of infection was 28%, including 5% with a driveline infection. Clinical hemolysis occurred in 6.7% of subjects, of which 60% of cases (4.3% of subjects) were associated with suspected thrombosis events, and the remainder (2.7% of subjects) were isolated hemolysis events that resolved either with treatment or on their own. None of the isolated hemolysis events resulted in subsequent PT.

Analysis of risk factors for PT

Table 5 shows a comparison between patients with and without PT for potential risk factors. No significant difference was observed between patients with and without thrombosis, although there was a trend toward significance in percentage of female patients in the group experiencing PT compared with the group without PT (33% vs 16%; $p = 0.15$). Besides sex, no difference in patients with and without PT was observed including age, indication, INTERMACS profile, and BMI (all $p > 0.05$).

Adherence to PREVENT recommendations

Figure 4 shows the adherence to the surgical recommendations. Of patients, 97% had their pumps implanted below the diaphragm, 99.7% had their inflow cannula placed parallel to the septum, 95% had their outflow graft placed such that it avoided the right ventricle, and 85% had their pumps anchored. Figure 4B shows an example of a pump implanted according to the surgical recommendations, and Figure 4C shows an example of a pump implanted that did not meet the recommendations. Pumps were implanted with adherence to all surgical recommendations in 78% of patients. A significant majority of the subjects were bridged with heparin (95%) to warfarin, and 100% of the subjects were anti-coagulated with warfarin, with a median INR of 2.1 (IQR 1.9–2.3). Median time spent in the recommended target range of 2.0–2.5 was 31% (IQR 19%–44%); however, only 3.9% (IQR 0%–17%) of the time was spent at INR <1.5 and 6.3% (IQR 0%–16%) of the time was spent at INR >3.0. Aspirin therapy was used in 82% ($n = 231$) of

Table 5 Univariable Analysis of Confirmed Pump Thrombosis Events

Characteristic	Subjects with PT ($n = 15$)	Subjects without PT ($n = 285$)	p-value
Age, years	57.2 ± 11.0	57.4 ± 12.9	0.71
Age >65	3 (20%)	97 (34%)	0.40
DT	12 (80%)	222 (78%)	1.00
Females	5 (33%)	47 (16%)	0.15
INTERMACS profiles			
Profile 1	1 (7%)	37 (13%)	0.54
Profile 2–3	13 (87%)	198 (69%)	
Profile 4–5	1 (7%)	50 (18%)	
Ischemic etiology	8 (53%)	131 (46%)	0.61
BMI	30.2 ± 4.9	29.4 ± 6.3	0.42
PCWP, mm Hg	21.6 ± 10.0 ($n = 13$)	24.2 ± 8.9 ($n = 238$)	0.24
Creatinine, mg/dl	1.49 ± 1.23	1.46 ± 0.75	0.27
CVP, mm Hg	10.8 ± 7.8 ($n = 12$)	12.2 ± 7.0 ($n = 229$)	0.37
History of atrial fibrillation	5 (33%)	89 (31%)	1.00
Known hypercoagulable disorder	1 (7%)	45 (16%)	0.48

BMI, body mass index; CVP, central venous pressure; DT, destination therapy; PCWP, pulmonary capillary wedge pressure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; PT, pump thrombosis.
Values are presented as mean ± SD or number (%).

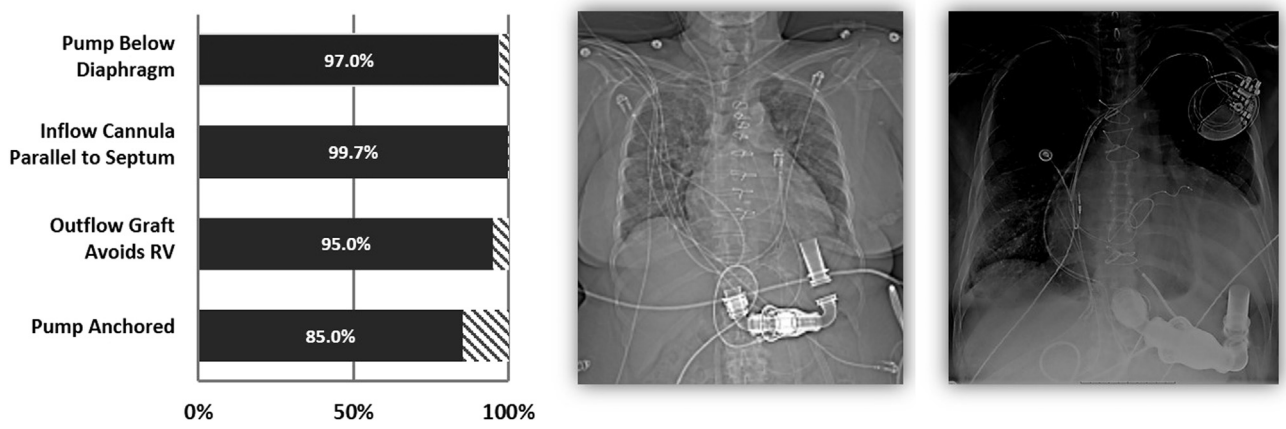

Figure 4 (A) Overall adherence to PREVENT surgical recommendations. (B) Example of a subject implanted adherent to the recommendations. (C) Subject implanted not adherent to the recommendations. RV, right ventricle.

the subjects ongoing with HMII at 30 days ($n = 282$). The remaining subjects ($n = 51$) were not on aspirin therapy predominantly because of peri-operative bleeding or center practice. An additional 21 patients had aspirin therapy stopped because of a later bleeding event. Median pump speed coming out of the operating room was 8,800 RPMs (IQR 8,600–9,000 RPMs), with only 68% of subjects with speeds $>8{,}600$ RPMs and 41% of subjects with speeds $\geq 9{,}000$ RPMs. By 30 days, median pump speeds had increased to 9,200 RPMs (IQR 9,000–9,400 RPMs), with 92% of subjects with speeds $>8{,}600$ RPMs and 79% of subjects with speeds $\geq 9{,}000$ RPMs. Average mean arterial pressure of patients was 85 mm Hg $\pm$ 10, with 72% of patients managed with an average mean arterial pressure <90 mm Hg. Figure 5 shows the number of sites that adhered to the key recommendations for most of their patients ($>80\%$) vs the sites that did not.

Adherence to PREVENT recommendations and impact on outcomes

Although the study was not powered to identify potential effects of individual components of practice recommendations, adherence to the specific recommendations and impact on PT were evaluated. Lack of the outflow graft

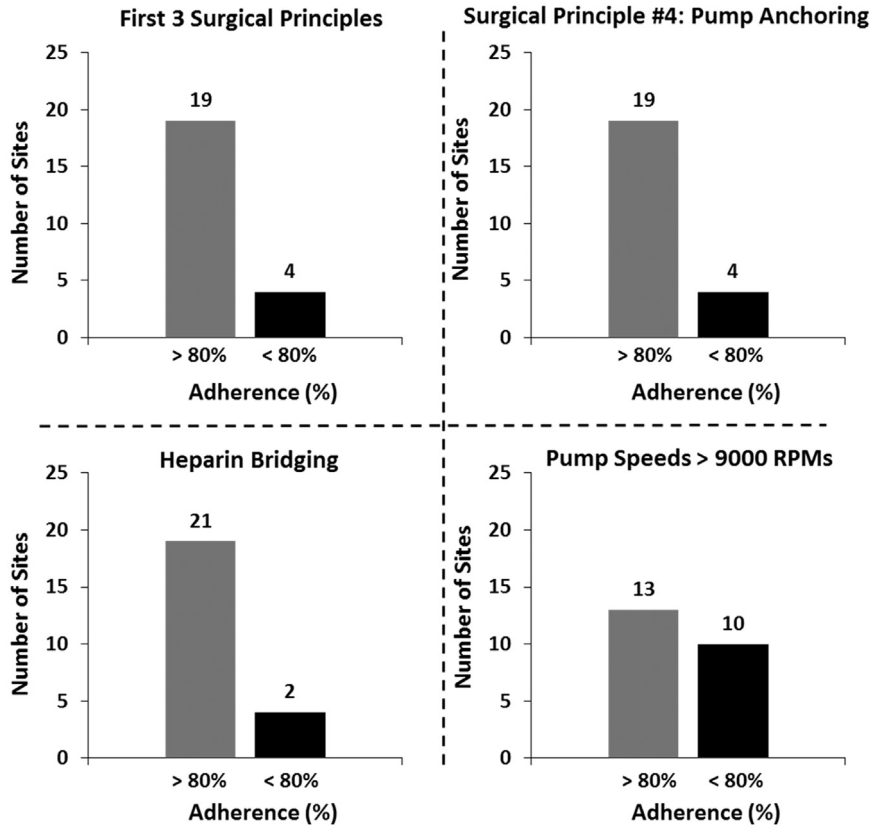

Figure 5 Number of sites that were able to adhere to the key PREVENT recommendations for $>80\%$ of their subjects.

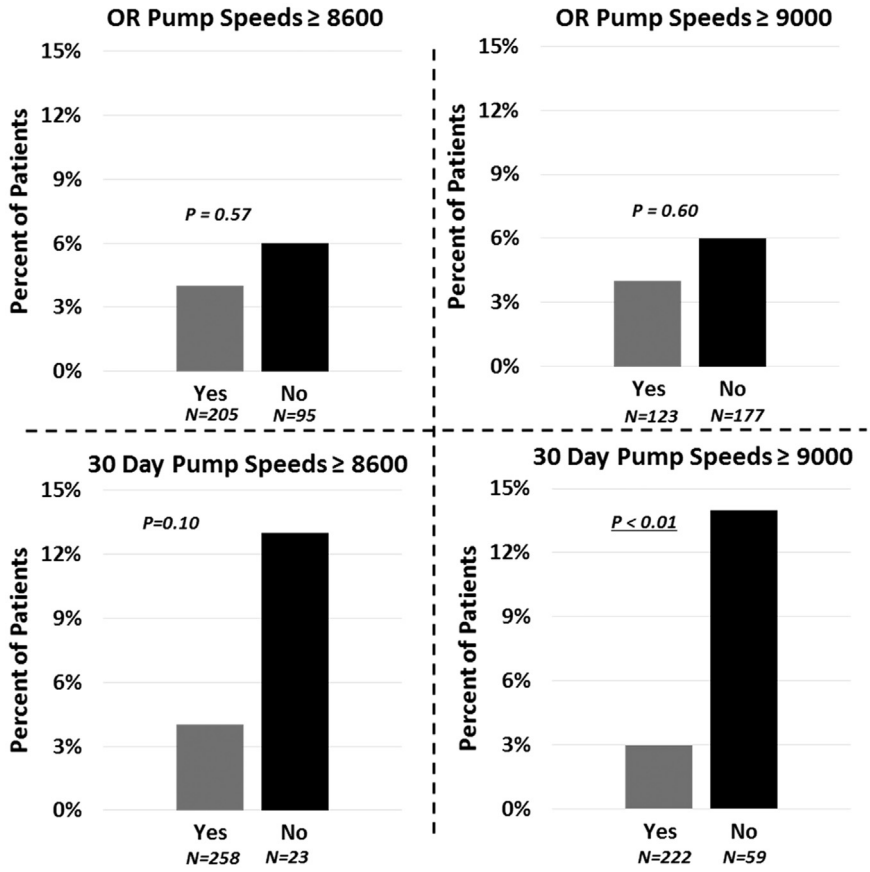

Figure 6 Percentage of patients with confirmed PT as a function of adherence to the PREVENT pump speed recommendations. OR, operating room.

not avoiding the right ventricle trended toward significance as a risk factor for PT (15% vs 5%; $p = 0.13$). Pump speeds coming out of the operating room did not have an impact on PT; however, patients with pump speeds <9,000 RPMs at 30 days had a significantly higher incidence of PT compared with patients who were managed with pump speeds ≥9,000 RPMs (14% vs 3%; $p < 0.01$ at 6 months, odds ratio 5.6 [confidence interval 1.9–17.0]) (Figure 6). At 30 days, there was no difference in estimated flow rates between patients with and without PT (6.3 liter/min ± 2.3 vs 5.5 liter/min ± 1.3; $p = 0.29$); however, estimated flow rates may be elevated in the setting of PT (owing to higher powers). There were no differences in mean arterial pressure (83 mm Hg ± 10 vs 85 mm Hg ± 10; $p = 0.57$) between patients with and without PT.

In patients in whom (1) 100% of the surgical recommendations were adopted, (2) heparin was used to bridge to warfarin with use of warfarin anti-coagulation, and (3) pump speed was ≥9,000 RPMs (good adherence), the rate of PT was significantly lower compared with patients in whom the recommendations were adhered to partially (1.9% vs 8.9% at 6 months; $p < 0.01$, odds ratio 5.0 [confidence interval 1.4–18.3]) (Figure 7). Similarly, the composite incidence of suspected thrombosis, hemolysis, or ischemic stroke was significantly lower in patients with good adherence compared with patients with partial adherence (5.7% vs 17.7% at 6 months, $p < 0.01$, odds ratio 3.6 [confidence interval 1.6–8.0]) (Figure 7). Additionally, where there was good adherence, patients had a significantly lower prevalence of elevated LDH at 30 days (LDH >2.5 times upper normal laboratory limit, as per most recent INTERMACS definition) compared with partial adherence (5.3% vs 14.0%; $p < 0.001$).

Discussion

The PREVENT trial met its primary end-point and demonstrated a lower rate of confirmed PT at 3 months after HMII device implantation (2.9%), lower than what was hypothesized (4%). The results demonstrated that an early (3 months) low incidence of PT could be achieved with adoption to a pre-determined set of surgical and medical recommendations. Despite the increased intensity of anti-coagulation, the incidence of reoperation for bleeding was comparable to previously published data.[1,18] Within the confines of this study population, no significant pre-operative risk factor was identified as increasing the risk of thrombosis except for female subjects, who trended toward having a higher risk of PT. This trend has been observed in previous studies as well.[19,20]

Although the study was not powered to show how each of the specific elements of the recommendations affect PT, patients managed with higher pump speeds (≥9,000 RPMs) did have a lower risk of PT. HMII has a mechanical bearing that is cooled by flowing blood. When flow rates are reduced to <3.8 liter/min,[21] the flow tends to become

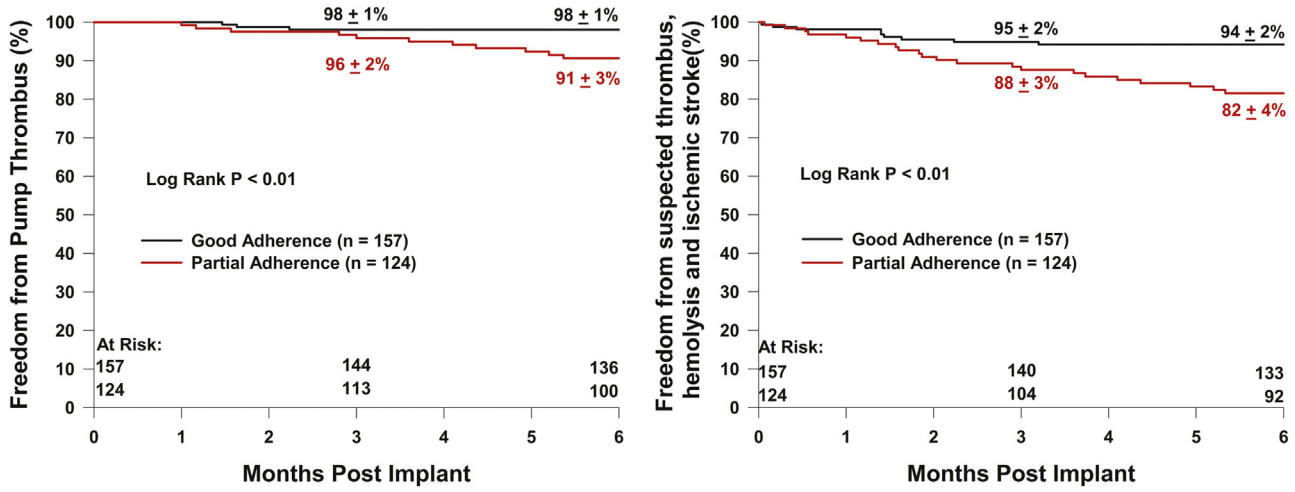

Figure 7 Freedom from confirmed PT and a composite of PT, hemolysis, and ischemic stroke in subjects with good adherence to the recommendations vs subjects with partial adherence.

chaotic, which may increase the risk of thrombus formation within the pump. The pressure-flow curves of the device indicate that a 4 liter/min flow rate can be achieved with a mean pressure differential of 65 mm Hg when the pump speed is at least 9,000 RPMs. At lower pump speeds (e.g., 8,000 RPMs), a pressure differential of 49 mm Hg is required to drive 4 liter/min through the pump. Hence if the patient is managed at a pump speed of $\geq$9,000 RPMs, the pump is more forgiving to increasing arterial pressures in maintaining flow. Additionally, the inability to achieve higher flow when running pumps at a higher speeds may be a sign of underlying mechanical obstruction resulting from sub-optimal inflow cannula positioning or right heart failure (which may predispose the pump to experience low flow conditions). The complex interplay that exists between surgical implantation and inflow cannula positioning along with early anti-coagulation and pump speeds necessitates that attention should be paid to all these recommendations to reduce the overall PT risk. Complete adherence to surgical recommendations, combined with post-operative heparin bridging, warfarin anti-coagulation, and speed settings $\geq$9000 RPMs, was independently associated with a decreased incidence of thromboembolic events 3 and 6 months after implantation.

Concerns regarding LVAD PT have been heightened as a result of 2 publications: (1) an initial report by investigators who documented an abrupt increase in the incidence of thrombosis of HMII at 3 months from 2.2% before March 2011 to 8.4% after January 2013 and (2) a detailed analysis of the INTERMACS database that reported a 6-fold increase in rates of PT in the time frame of 2011–2012.[3,4] Furthermore, the 6-month actuarial freedom from device exchange or death resulting from PT has significantly decreased from 99% in the 2008–2009 to 95% in 2011, 93% in 2012, and 92% in 2013.[4] Other reports pertaining to PT with continuous-flow LVADs, some with differing opinions on the incidence of thrombosis [22–24] and others with single-center experiences with higher incidence of PT, have started to emerge as well.[6,12,25–28] Although not intended for direct comparisons with these reports, the results of the PREVENT multi-center study differed from these observations and demonstrated that uniform adoption of simple clinical practice management recommendations can significantly reduce the incidence of PT. Adopting an aggressive anti-coagulation strategy including heparin bridging post-operatively appears to be critical to mitigate the early occurrence of PT and is not associated with increased risk of reoperation for bleeding. A recent update to the INTER-MACS registry has demonstrated that there has been a trend toward a reduction in PT events, possibly as a result of the independent adoption of principles outlined in our study.[20] A subset of patients without aspirin therapy did not experience an increased incidence of PT, and this may represent an area for future analysis in the planned PREVENT II trial.

The issue of PT remains a challenge for the field and is not unique to the current era or current pumps. Mehra et al[29] eloquently captured the essence of the problem of PT by reminding us: "The law of unintended consequences posits that a simple intervention within a complex system always creates unanticipated and often undesirable outcomes." Issues of biocompatibility continue to be at the forefront of design considerations in the development of new pumps, and the field of mechanical circulatory support must focus on adopting a standardized approach to this therapy so that valid analyses and comparisons can be made. However, until new designs can be fully evaluated and prove themselves as superior, best practices should be developed and implemented to control known risks. We propose a structured set of collaboratively developed principles and recommendations that are now shown to significantly improve outcomes. Future efforts will need to demonstrate if these recommendations, when used, can lead to similar improvements in programs that were not part of this study.

No society guidelines or consensus statements exist regarding the diagnosis or management of LVAD PT despite the potential morbidity and mortality conferred by this clinical entity. In 2013, a working group examining the issue of LVAD PT proposed an algorithm for the diagnosis and management of PT.[30] Patients may present with various

conditions, including (1) pump power elevations, (2) isolated increase in LDH, (3) evidence of hemolysis, or (4) new heart failure symptoms. However, intermittent power elevations may often occur early post-operatively and have not been identified as having an impact on PT.[31]

Although this study was not designed to address optimal PT treatment strategies, a low mortality was observed in patients with confirmed PT when treated by center preferences. The optimal treatment and primary approach for a patient with PT have not been fully established and remain a source of continued debate. In hemodynamically stable patients, medical therapy is often employed initially, which most commonly includes high-dose unfractionated heparin and fluid resuscitation and sometimes involves the addition of glycoprotein IIb/IIIA inhibitors and/or thrombolytics. Although small series demonstrated a high success rate with low morbidity, an analysis of larger series demonstrated success rates of 23%–50%, stroke rates of 10%–15%, bleeding complication rates of 65%, and higher mortality rates of 17%–52%.[32–34] Even in the face of "successful medical therapy," there is an accompanying high morbidity burden. The present study underlines the benefits of early surgical intervention, with a high success rate (pump exchange, heart transplantation) with acceptable morbidity. Further studies designed to address this specific issue need to be elaborated.

The study has limitations. Although singular in protocol, the multi-center nature of this study allowed the introduction of variability in practices among institutions. All centers included in this study agreed to adhere to surgical and medical recommendations, but the status of how centers used and managed patients before the study enrollment was unknown and unavailable for comparison. Likewise, because of variability in PT definitions among centers, the rates of PT before initiation of the clinical study were unavailable for direct comparison. During the study period, other durable device studies were concomitantly recruiting patients, which may have allowed for selection bias. The lack of randomization weakens the study analysis, but the investigators believe that the large historical and reported clinical experience with HMII validates the design of the study. This was a non-randomized study, and there was no formal control group in the study. Results were compared with a pre-defined thrombus rate. Also, factors related to risk of thrombus are limited to the patient population enrolled in the study, where the range of factors was controlled by protocol. Finally, this study evaluated the risk of early PT only. Studies with longer follow-up are needed to assess the impact of these recommendations on long-term PT.

In conclusion, a structured surgical implant and subsequent clinical management practice pathway is feasible in most patients, and adherence to those recommendations is associated with a low incidence of early PT with HMII. The results emphasize the importance of LVAD implantation techniques to create an unobstructed blood flow path, maintenance of adequate anti-coagulation including post-operative heparin bridging, and early optimal speed management ($\geq$ 9,000 RPMs).

Disclosure statement

S.M. and N.U. report consulting activity for St. Jude Medical, Inc., and HeartWare. A.K., S.E., B.S., R.A., and I.G. report consulting activity for St. Jude Medical, Inc. J.B.O., D.J.F., and K.S.S. are employed by St. Jude Medical, Inc. S.N., M.K., J.R., J.N.K., A.B., G.E., J.W.E., and J.S. have no conflicts to report.

The authors thank Dr. Francis D. Pagani from the University of Michigan and Dr. Joseph G. Rogers from Duke University for adjudicating the suspected pump thrombosis events. The authors also thank Dr. Jennifer Cowger from St. Vincent's Heart Center of Indiana, Dr. James Long from Integris Baptist Hospital, Dr. Charles Klodell (PREVENT Investigator), Dr. Nir Uriel (PREVENT Investigator and Author), and Dr. Jason Katz (PREVENT Investigator and Author) for serving on the protocol development committee for the PREVENT study.

References

1. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2011;57:1890-8.
2. Stulak JM, Davis ME, Haglund N, et al. Adverse events in contemporary continuous-flow left ventricular assist devices: a multi-institutional comparison shows significant differences. J Thorac Cardiovasc Surg 2016;151:177-89.
3. Starling RC, Moazami N, Silvestry SC, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med 2014;370:33-40.
4. Kirklin JK, Naftel DC, Kormos RL, et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. J Heart Lung Transplant 2014;33:12-22.
5. Stulak JM, Sharma S, Maltais S. Management of pump thrombosis in patients with left ventricular assist devices. Am J Cardiovasc Drugs 2015;15:89-94.
6. Stulak JM, Maltais S. A different perspective on thrombosis and the HeartMate II. N Engl J Med 2014;370:1467-8.
7. Najjar SS, Slaughter MS, Pagani FD, et al. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. J Heart Lung Transplant 2014;33:23-34.
8. Crow S, John R, Boyle A, et al. Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. J Thorac Cardiovasc Surg 2009;137:208-15.
9. Uriel N, Pak SW, Jorde UP, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol 2010;56:1207-13.
10. Cowger J, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolias TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. Circ Heart Fail 2010;3:668-74.
11. Taghavi S, Ward C, Jayarajan SN, Gaughan J, Wilson LM, Mangi AA. Surgical technique influences HeartMate II left ventricular assist device thrombosis. Ann Thorac Surg 2013;96:1259-65.
12. Uriel N, Han J, Morrison KA, et al. Device thrombosis in HeartMate II continuous-flow left ventricular assist devices: a multifactorial phenomenon. J Heart Lung Transplant 2014;33:51-9.
13. Adamson RM, Bower BL, Sundareswaran KS, Farrar DJ, Dembitsky WP. Radiologic assessment of HeartMate II position: minimal pump migration after long-term support. J Heart Lung Transplant 2015;34:1617-23.
14. Adamson RM, Mangi AA, Kormos RL, Farrar DJ, Dembitsky WP. Principles of HeartMate II implantation to avoid pump malposition and migration. J Card Surg 2015;30:296-9.

15. Klodell CT, Massey HT, Adamson RM, et al. Factors related to pump thrombosis with the Heartmate II left ventricular assist device. J Card Surg 2015;30:775-80.
16. Heatley G, Sood P, Goldstein D, et al. Clinical trial design and rationale of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) investigational device exemption clinical study protocol. J Heart Lung Transplant 2016;35:528-36.
17. Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant 2015;34: 1495-504.
18. Jorde UP, Kushwaha SS, Tatooles AJ, et al. Results of the destination therapy post-Food and Drug Administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS Registry (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2014;63:1751-7.
19. Boyle AJ, Jorde UP, Sun B, et al. Pre-operative risk factors of bleeding and stroke during left ventricular assist device support: an analysis of more than 900 HeartMate II outpatients. J Am Coll Cardiol 2014;63:880-8.
20. Kirklin JK, Naftel DC, Pagani FD, et al. Pump thrombosis in the Thoratec HeartMate II device: an update analysis of the INTERMACS Registry. J Heart Lung Transplant 2015;34:1515-26.
21. Yang F, Kormos RL, Antaki JF. High-speed visualization of disturbed pathlines in axial flow ventricular assist device under pulsatile conditions. J Thorac Cardiovasc Surg 2015;150:938-44.
22. Klodell CT, Massey HT, Adamson R, et al. Factors related to pump thrombosis at select medium to high volume centers. Paper presented at: 34th Annual Meeting and Scientific Sessions, International Society of Heart and Lung Transplantation. April 10–13, 2014; San Diego, CA.
23. Hoefer D, Velik-Salchner C, Antretter H. Increase in left ventricular assist device thrombosis. N Engl J Med 2014;370:1464.
24. Schmitto JD, Avsar M, Haverich A. Increase in left ventricular assist device thrombosis. N Engl J Med 2014;370:1463-4.
25. Al-Quthami AH, Jumean M, Kociol R, et al. Eptifibatide for the treatment of HeartMate II left ventricular assist device thrombosis. Circ Heart Fail 2012;5:e68-70.
26. Bashir J, Cheung A, Kaan A, Kearns M, Ibey A, Ignaszewski A. Thrombosis and failure of a HeartMate II device in the absence of alarms. J Heart Lung Transplant 2011;30:1197-9.
27. Ravichandran AK, Parker J, Novak E, et al. Hemolysis in left ventricular assist device: a retrospective analysis of outcomes. J Heart Lung Transplant 2014;33:44-50.
28. Stulak JM, Lee D, Haft JW, et al. Gastrointestinal bleeding and subsequent risk of thromboembolic events during support with a left ventricular assist device. J Heart Lung Transplant 2014;33:60-4.
29. Mehra MR, Stewart GC, Uber PA. The vexing problem of thrombosis in long-term mechanical circulatory support. J Heart Lung Transplant 2014;33:1-11.
30. Kirkin JK, Naftel DC, Kormos RL, et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. J Heart Lung Transplant 2014;33:12-22.
31. Salerno CT, Sundareswaran KS, Schleeter TP, Moanie SL, Farrar DJ, Walsh MN. Early elevations in pump power with the HeartMate II left ventricular assist device do not predict late adverse events. J Heart Lung Transplant 2014;33:809-15.
32. Kamouh A, John R, Eckman P. Successful treatment of early thrombosis of HeartWare left ventricular assist device with intra-ventricular thrombolytics. Ann Thorac Surg 2012;94:281-3.
33. Schlendorf K, Patel CB, Gehrig T, et al. Thrombolytic therapy for thrombosis of continuous flow ventricular assist devices. J Card Fail 2014;20:91-7.
34. Stulak JM, Dunlay SM, Sharma S, et al. Treatment of device thrombus in the HeartWare HVAD: success and outcomes depend significantly on the initial treatment strategy. J Heart Lung Transplant 2015;34: 1535-1541.